II.C.2.

In 1982, a market research report for Imperial Tobacco Ltd., BATCO's Canadian subsidiary, referred to attitudes of adolescents "[o]nce addiction does take place," and states that "addicted they do indeed become."[526] The report goes on:

> Recidivism has several causes . . . [including] the belief that after a few weeks off cigarettes, one could begin again to smoke 'just a few.' . . . This 'just a few' business is actually *a surrender to addiction* while trying to . . . *pretend to oneself and to others that addiction is no longer present, which is nonsense.*[527]

At a 1983 BATCO research conference, the minutes of the proceedings state that "*[t]he basic assumption is that nicotine . . . is almost certainly the key smoke component for satisfaction . . .*"[528]

In a 1984 letter, C. I. Ayres of BATCO wrote to E. E. Kohnhorst, the executive vice president and chief operating officer of Brown & Williamson, enclosing a report stating that nicotine is "why people inhale smoke":

> *It is well known that nicotine can be removed from smoke by the lung and transmitted to the brain within seconds of smoke inhalation.* Since it is the major or sole pharmacologically active agent in smoke, *it must be presumed that this is its preferred method of absorption and thus why people inhale smoke.*[529]

In 1984, BATCO also held two research conferences at which nicotine was extensively discussed. At the first conference, BATCO researchers held sessions on

---

[526] Kwechansky Marketing Research (report prepared for Imperial Tobacco Ltd.), *Project Plus/Minus* (May 7, 1982), at i, 26 (emphasis added). *See* AR (Vol. 108 Ref. 1571).

[527] *Id.* at 36-37 (emphasis added).

[528] Minutes of BATCO Research Conference at Rio de Janeiro (Aug. 22-26, 1983), at 10 (emphasis added). *See* AR (Vol. 179 Ref. 2087).

[529] Greig CC, *Short Lived Species in Smoke* (Jan. 26, 1984), attached to letter from Ayres CI (BATCO) to Kohnhorst EE (Brown & Williamson) (Feb. 9, 1984), at 10 (emphasis added). *See* AR (Vol. 34 Ref. 584).

"Nicotine Dose Requirement-Background," "Nicotine Dose Estimation," "Effects of Nicotine—Interaction with the Brain (Pharmacology)," and "Product Modification for Maximal Nicotine Effects."[530] The researchers reported that *"[i]ntuitively it is felt that 'satisfaction' must be related to nicotine. Many people believe it [is] a 'whole body response' and involves the action of nicotine in the brain."*[531] They also acknowledged *"the central role of nicotine in the smoking process and our business generally."*[532]

At the second conference, BATCO researchers reported that *"in its simplest sense puffing behaviour is the means of providing nicotine dose in a metered fashion."*[533] According to one BATCO researcher speaking at the conference:

> Smoking is . . . a personal tool used by the smoker to refine his behaviour and reactions to the world at large.
>
> It is apparent that *nicotine largely underpins these contributions through its role as a generator of central physiological arousal effects* which express themselves as changes in human performance and psychological well-being."[534]

Other similar statements are summarized in the Jurisdictional Analysis. *See* 60 FR 41584-41666. Like the statements quoted above, they show that scientists at Brown &

---

[530] Ayres CI (BATCO), Notes from the GR&DC [Group Research and Development Centre] Nicotine Conference at Southampton, England (Jul. 9-12, 1984) (slide), at BW-W2-02639. *See* AR (Vol. 14 Ref. 172).

[531] Minutes of BATCO Nicotine Conference at Southampton, England (Jun. 6-8, 1984), at BW-W2-01977 (emphasis added). *See* AR (Vol. 22 Ref. 287-6).

[532] Ayres CI (BATCO), Notes from the GR&DC [Group Research and Development Centre] Nicotine Conference at Southampton, England (Jul. 9-12, 1984), at 62 (emphasis added). *See* AR (Vol. 14 Ref. 172-1).

[533] Proceedings of BATCO Group R&D Smoking Behaviour-Marketing Conference, Session I (Jul. 9-12, 1984) (slide), at BW-W2-03242 (emphasis added). *See* AR (Vol. 21 Ref. 238).

[534] Ferris RP, *The role of smoking behaviour in product development: some observations on the psychological aspects of smoking behaviour,* in Proceedings of BATCO Group R&D Smoking Behaviour-Marketing Conference, Session III (Jul. 9-12, 1984), at 79 (emphasis added). *See* AR (Vol. 192 Ref. 2172).

Williamson and BATCO devoted extensive attention to understanding the pharmacological effects and uses of nicotine, consistently regarded nicotine as being the primary reason consumers smoked, and viewed cigarettes as nicotine delivery devices.

iii. Statements and Research in the 1990's. New documents received by FDA during the public comment period demonstrate that researchers and officials of Brown & Williamson and BATCO continue to hold similar views about nicotine in cigarettes in the 1990's. The new documents are a series of memoranda relating to the potential purchase in 1992 by BATCO of a manufacturer of nicotine patches, Stowic Resources Ltd.[535]

Brown & Williamson's research department evaluated the potential purchase in a memorandum entitled "Transdermal Nicotine Patches." Brown & Williamson researchers observed that "[t]here is currently a void in the market for a product that provides tobacco satisfaction in a form that is acceptable and available to many segments of the market" and recommended that "[w]e should be looking for opportunities to fill the void."[536] However, Brown & Williamson researchers expressed doubts that a nicotine patch could provide consumers with the same pharmacological effects obtained by smoking:

> The pattern of the blood nicotine concentrations attained by smoking vs the patch, however, are different. *With smoking, blood nicotine absorption is very rapid.* Blood nicotine concentrations go through a series of peaks and troughs with successive cigarette smoking throughout the day. . . . With the patch, nicotine absorption is relatively slow and continuous and peak blood levels are not as high as with cigarette smoking. *A major advantage of cigarette smoking over the nicotine patch system is the ability for*

[535] Salter R, *Transdermal Nicotine* (Apr. 3, 1992); Research and Development, *Response to BAT Industries Note on Transdermal Nicotine (28.02.92)* (Mar. 27, 1992); Kausch, Research and Development/Quality, *Transdermal Nicotine;* Research and Development/Quality, *Transdermal Nicotine Patches*; McGraw M (Brown & Williamson), *Nicotine Delivery Systems* (Apr. 24, 1992). *See* AR (Vol. 531 Ref. 124).

[536] *Transdermal Nicotine Patches*, at 3. *See* AR (Vol. 531 Ref. 124).

*the smoker to have very flexible control over titrating his desired dose of nicotine.*[537]

Similar views were expressed by other BAT Industries subsidiaries. BAT Industries' German subsidiary, for instance, stated that "*[t]he rapid, peaking intake of nicotine which the smoker clearly wants cannot be achieved with nicotine application via . . . plaster.*"[538]

The German subsidiary further acknowledged that nicotine can produce dependency and addiction. According to the German report, which was distributed by BAT Industries to the then president of Brown & Williamson, R. J. Pritchard, "*[t]he disadvantage of rapid nicotine intake similar to that achieved with a cigarette is seen in the danger of people possibly becoming dependent on it.*"[539] The German subsidiary observed that even with nicotine gum there is a "*danger of addiction,*" stating that "the smoker can organize intake to suit himself" and achieve "[a]ctive control over intake and the condition it produces."[540]

Brown & Williamson's legal department argued against the purchase of Stowic on legal grounds, warning that it would suggest that Brown & Williamson is in "the nicotine delivery business" and cause Brown & Williamson to "*run a serious risk of facing FDA jurisdiction.*" The lawyers also argued that the purchase of Stowic would have "disastrous" implications for product liability litigation because "*[t]he marketing of any*

---

[537] *Id.* at 2 (emphasis added).

[538] Research and Development/Quality, *Re: Transdermal Nicotine*, at 3 (emphasis added). *See* AR (Vol. 531 Ref. 124).

[539] *Id.* at 3 (emphasis added).

[540] *Id.* at 2.

*nicotine delivery system undercuts our position on addiction.*"[541] Ultimately, BAT Industries rejected the purchase of Stowic.

iv. The Wigand Deposition. A comment from public health organizations has also urged FDA to consider a 1995 deposition of Jeffrey S. Wigand, the vice president of research and development at Brown & Williamson from 1989 to 1993. According to Wigand's deposition, which was submitted to the Agency with the comment, and which has been widely publicized in the media, a number of officers of Brown & Williamson, including Thomas Sandefur, the company president and chief executive officer, made "numerous statements . . . that *we're in the nicotine delivery business.*"[542] Wigand also testified in the deposition that Sandefur "frequently" stated the opinion and belief that nicotine is "*addictive*";[543] that Brown & Williamson manipulates nicotine levels in tobacco, using various techniques including blending of tobacco leaves and adding ammonia compounds to change the pH of smoke;[544] that BATCO scientists had done studies to identify "the boundaries of nicotine pharmacology," and that BATCO showed that nicotine below "0.4 milligrams does not sustain satisfaction."[545]

---

[541] McGraw M (Brown & Williamson), *Nicotine Delivery Systems* (Apr. 24, 1992), at 1-2 (emphasis added). *See* AR (Vol. 531 Ref. 124).

[542] Deposition transcript of Wigand JS (Nov. 29, 1995), at 12 (emphasis added). *See* AR (Vol. 700 Ref. 224, exhibit 2).

[543] *Id.* at 12-13.

[544] *Id.* at 27-29.

[545] *Id.* at 27, 33.

Wigand's assertions in the deposition have been disputed by Brown & Williamson, which contends that they are untrue.[546] His statements, however, are consistent with and corroborated by the views expressed by Brown & Williamson and BAT Industries officials since the 1960's. Although the Agency finds Wigand's testimony to be additional relevant evidence of the manufacturers' intent to affect the structure and function of the body, his testimony is not essential to any of the Agency's determinations.

Cumulatively, the three decades of documents from Brown & Williamson, BATCO, and BAT Industries demonstrate that these companies have long understood that nicotine is addictive and has other significant pharmacological effects; that consumers smoke cigarettes to obtain the drug effects of nicotine; and that cigarettes are a drug delivery system, functioning as "the means of providing nicotine in a metered fashion."[547]

### d. The Statements and Research of Other Cigarette Manufacturers

The administrative record establishes that the other major cigarette companies, the American Tobacco Company, the Lorillard Tobacco Company, and the Liggett Group Inc., funded research studies similar to the research conducted by Philip Morris, RJR, and Brown & Williamson, and as a result of the research have acquired a detailed knowledge of the pharmacological effects of nicotine on the brain.

For instance, American Tobacco which merged with Brown & Williamson in 1995, funded extensive research on nicotine pharmacology. From 1940 through 1970, American

---

[546] *See, e.g.*, Freedman AM, Cigarette defector says CEO lied to Congress about view of nicotine, *Wall Street Journal*, Jan. 26, 1996. *See* AR (Vol. 639 Ref. 2).

[547] Proceedings of BATCO Group R&D Smoking Behaviour Marketing Conference, Session I (Jul. 9-12, 1984) (slide), at BW-W2-03242. *See* AR (Vol. 24 Ref. 316).

Tobacco funded 111 studies on the biological effects of cigarettes.[548] According to a staff report of the House Subcommittee on Health and the Environment, ninety-three of these studies (over 80%) related to the effects of nicotine on the body.[549] In one 1945 study funded by the company, entitled "The Role of Nicotine in the Cigarette Habit," smokers were given cigarettes with extremely low levels of nicotine. The study found that half of the subjects "definitely missed the nicotine."[550]

The activities of the Council for Tobacco Research (CTR), an industry trade association that conducts research on behalf of the major tobacco producers in the United States,[551] are further evidence of the extent of the industry's knowledge of the pharmacological effects of nicotine on the human brain. On behalf of the tobacco industry, CTR has funded numerous studies on the pharmacology of nicotine. The goal of these studies was to learn why nicotine makes people want to smoke:

> Most of the pharmacological studies currently being supported by The Council are concerned with the effects of nicotine and/or smoking on the central nervous system (the brain) with *the object of learning more about why people like, want or need to smoke.*[552]

---

[548] Staff Report, *Evidence of Nicotine Manipulation by the American Tobacco Company*, and exhibits, prepared by the Majority Staff Subcommittee on Health and the Environment (Dec. 20, 1994), at 3. *See* AR (Vol. 292 Ref. 4064-4066).

[549] *Id.*

[550] Finnegan JK, Larson PS, Haag HB (American Tobacco Co.), The role of nicotine in the cigarette habit, in *Biologic Research on Tobacco* (American Tobacco Company: 1962), at 65-66 (originally published in *Science* 1945;102). *See* AR (Vol. 14 Ref. 178-1).

[551] All the major cigarette manufacturers have participated in CTR. The current members include Philip Morris, R.J. Reynolds, Brown & Williamson, and Lorillard Tobacco Co. Although the Liggett Group is not currently a member of CTR, it has been so in the past. *See* Letter from Yeaman to Ahrensfeld *et al.* of Dec. 6, 1977. *See* AR (Vol. 478 Ref. 8069).

[552] Council for Tobacco Research, *Report of the Scientific Director, 1969-1970*, at 13 (emphasis added). *See* AR (Vol. 16 Ref. 195-4).

II.C.2.

The body of CTR research on nicotine pharmacology is extensive. For example:

- Thirty-nine CTR studies identify the sites and mechanisms of nicotine receptors in the brain;[553]

[553] These CTR documents, along with the other CTR documents cited in this section, can be found in the administrative record, Volumes 45-64 of Docket 95N0253J:

Abood LG, Grassi S, Noggle HD, Comparison of the binding of optically pure (-)- and (+)-[3H] nicotine to rat brain membranes, *Neurochem Res* 1985;10(2):259-267.

Abood LG, Lowy K, Tometsko A, *et al.*, Electrophysiological, behavioral, and chemical evidence for a noncholinergic, stereospecific site for nicotine in rat brain, *J Neurosci Res* 1978;3(5-6):327-333.

Abood LG, Lowy K, Tometsko A, *et al.*, Evidence for a noncholinergic site for nicotine's action in brain: Psychopharmacological, electrophysiological and receptor binding studies, *Arch Int Pharmacodyn Ther* 1979;237(2):213-229.

Abood LG, Grassi S, Tritiated Methylcarbamylcholine a new radioligand for studying brain nicotinic receptors, *Biochem Pharmacol* 1990;35(23):4199-4202.

Andersson K, Siegel R, Fuxe K, *et al.*, Intravenous injections of nicotine induce very rapid and discrete reductions of hypothalamic catecholamine levels associated with increases of ACTH, vasopressin, and prolactin secretion, *Acta Physiol Scand* 1983;118(1 )35-40.

Andersson K, Fuxe K, Eneroth P, *et al.*, Effects of acute central and peripheral administration of nicotine on hypothalamic catecholamine nerve terminal systems and on the secretion of adenohypophyseal hormones in the male rat, *Med Biol* 1982;60(2):98-111.

Andersson K, Eneroth P, Agnati LF, Nicotine-induced increases of noradrenaline turnover in discrete noradrenaline nerve terminal systems of the hypothalamus and the median eminence of the rat and their relationship to changes in the secretion of adenohypophyseal hormones, *Acta Physiol Scand* 1981; 113:227-231.

Andersson K, Fuxe K, Agnati LF, Effects of single injections of nicotine on the ascending dopamine pathways in the rat. Evidence for increases of dopamine turnover in the mesostriatal and mesolimbic dopamine neurons, *Acta Physiol Scand* 1981;112(3):345-347.

Andersson K, Fuxe K, Agnati LF, *et al.*, Effects of acute central and peripheral administration of nicotine on ascending dopamine pathways in the male rat brain. Evidence for nicotine induced increases of dopamine turnover in various telencephalic dopamine nerve terminal systems, *Med Biol* 1981;59(3): 170-176.

Britto LR, Keyser KT, Lindstrom JM, *et al.*, Immunohistochemical localization of nicotinic acetylcholine receptor subunits in the mesencephalon and diencephalon of the chick (Gallus gallus), *J Comp Neurol* 1992;317(4):325-340.

Chance WT, Kallman MD, Rosecrans JA, *et al.*, A comparison of nicotine and structurally related compounds as discriminative stimuli, *Br J Pharmacol* 1978;63(4):609-616.

Davies BD, Hess W, Lin JP, *et al.*, Evidence for a noncholinergic nicotine receptor on human phagocytic leukocytes, *Mol Cell Biochem* 1982;44(1):23-31.

Fuxe K, Andersson K, Eneroth P, *et al.*, Neuroendocrine actions of nicotine and of exposure to cigarette smoke: medical implications, *Psychoneuroendocrinology* 1989;14(1-2):19-41.

Fuxe K, Andersson K, Eneroth P, *et al.*, Neurochemical mechanisms underlying the neuroendocrine actions of nicotine: focus on the plasticity of central cholinergic nicotinic receptors, *Prog Brain Res* 1989;79:197-207.

Harfstrand A, Adem A, Fuxe K, *et al.*, Distribution of nicotinic cholinergic receptors in the rat tel-and diencephalon: a quantitative receptor autoradiographical study using [3H]-acetylcholine, [alpha-1251] bungarotoxin and [3H] nicotine, *Acta Physiol Scand* 1988;132(1):1-14.

Huganir RL, Delcour AH, Greengard P, *et al.*, Phosphorylation of the nicotinic acetylcholine receptor regulates its rate of desensitization, *Nature* 1986;321:774-776.

Lapin EP, Maker HS, Sershen H, *et al.*, Action of nicotine on accumbens dopamine and attenuation with repeated administration, *Eur J Pharmacol* 1989:160(1):53-59.

Lindstrom J, Schoepfer R, Conroy WG, *et al.*, Structural and functional heterogeneity of nicotinic receptors, in *The Biology of Nicotine Dependence*, eds. Bock G, Marsh J, Ciba Foundation Symposium 1990:23-42, 152.

Lukas RJ, Heterogeneity of high-affinity nicotinic [3H]acetylcholine binding sites, *J Pharmacol Exp Ther* 1990;253(1):51-57.

Lukas RJ, Pharmacological distinctions between functional nicotinic acetylcholine receptors on the PC12 rat pheochromocytoma and the TE671 human medulloblastoma, *J Pharmacol Exp Ther* 1989;251(1):175-182.

Marks MJ, Collins AC, Characterization of nicotine binding in mouse brain and comparison with the binding of alpha-bungarotoxin and quinuclidinyl benzilate, *Mol Pharmacol* 1982:554-564.

Martin BR, Aceto MD, Nicotine binding sites and their localization in the central nervous system, *Neurosci Biobehav Rev* 1981;5:473-478.

Mitchell SN, Smith KM, Joseph MH, *et al.*, Increases in tyrosine hydroxylase messenger RNA in the locus coeruleus after a single dose of nicotine are followed by time-dependent increases in enzyme activity and noradrenaline release, *Neuroscience* 1993;56(4):989-997.

Mitchell SN, Role of the locus coeruleus in the noradrenergic response to a systemic administration of nicotine, *Neuropharmacology* 1993;32(10):937-949.

Owman C, Fuxe K, Janson AM, *et al.*, Chronic nicotine treatment eliminates asymmetry in striatal glucose utilization following unilateral transection of the mesostriatal dopamine pathway in rats, *Neurosci Lett* 1989;102(2-3):279-283.

Pradhan SN, Bowling C, Effects of nicotine on self-stimulation in rats, *J Pharmacol Exp Ther* 1971;176(1):229-243.

Rosecrans JA, Nicotine as a discriminative stimulus: a neurobehavioral approach to studying central cholinergic mechanisms, *J Subst Abuse* 1989;1(3):287-300.

- Thirty-six CTR studies show that nicotine produces neurochemical and metabolic effects in the brain;[554]

---

Rosecrans JA, Noncholinergic mechanisms involved in the behavioral and stimulus effects of nicotine, and relationships to the process of nicotine dependence, in *Tobacco Smoking and Nicotine: A Neurobiological Approach*, eds. Martin WR, Van Loo GR, Iwamoto ET, *et al.*, 1987:125-139.

Schaeppi U, Nicotine treatment of selected areas of the cat brain: effects upon EEG and autonomic system, *Int J Neuropharmacol* 1968;7(3):207-220.

Sershen H, Lajtha A, Nicotinic Binding Sites in the brain: properties, regulation, and putative endogenous ligands, in, *Tobacco Smoking and Nicotine: A Neurobiological Approach, eds.* Martin WR, Van Loo GR, Iwamoto ET, *et al.*, 1987:481-491.

Sershen H, Reith ME, Lajtha A, *et al.*, Noncholinergic, saturable binding of (+/-)-[3H] nicotine to mouse brain, *J Recept Res* 1981:1-15.

Sorenson EM, Gallagher JP, The reducing agent dithiothreitol (DTT) does not abolish the inhibitory nicotinic response recorded from rat dorsolateral septal neurons, *Neurosci Lett* 1993;152(1-2):137-140.

Stitzer M, Morrison J, Domino EF, Effects of nicotine on fixed-interval behavior and their modification by cholinergic antagonists, *J Pharmacol Exp Ther* 1970;171(2):166-177.

Sugiyama H, Hagino N, Moore G, *et al.*, [3-H] Nicotine binding sites in developing fetal brains in rats, *Neurosci Res*1985;2(5):387-392.

Svensson TH, Grenhoff J, Engberg G, Effect of nicotine on dynamic function of brain catecholamine neurons, in The *Biology of Nicotine Dependence*, eds. Bock G, Marsh J., *CIBA Foundation Symposium* 1990;152:169-180.

Toth E, Vizi ES, Lajtha A, Effect of nicotine on levels of extracellular amino acids in regions of the rat brain in vivo, *Neuropharmacology* 1993;32(8):827-832.

Whiting PJ, Schoepfer R, Conroy WG, *et al.*, Expression of nicotinic acetylcholine receptor subtypes in brain and retina, *Brain Res Mol Brain Res* 1991;10(1):61-70.

Wong LA, Gallagher JP, A direct nicotinic receptor-mediated inhibition recorded intracellularly in vitro, *Nature* 1989;341(6241):439-442.

Wong LA, Gallagher JP, Pharmacology of nicotinic receptor-mediated inhibition in rat dorsolateral septal neurones, *J Physiol (Lond)* 1991;436:325-346.

[554] Andersson K, Fuxe K, Agnati LF, *et al.*, Effects of acute central and peripheral administration of nicotine on ascending dopamine pathways in the male rat brain. Evidence for nicotine induced increases of dopamine turnover in various telencephalic dopamine nerve terminal systems, *Med Biol* 1981;59(3):170-176.

Andersson K, Mecamylamine pretreatment counteracts cigarette smoke induced changes in hypothalamic catecholamine neuron systems and in anterior pituitary function, *Acta Physiol Scand* 1985;125(3):445-452.